DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

AUG - 7 1997

Deputy Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Premarket Approval of Abbott Laboratories'
IMx® PSA and AxSYM® PSA - ACTION

The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA supplement.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Kimber C. Richter

Kimber C. Richter, M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved ✓ Disapproved _____ Date 8/7/97

Prepared by James P. Reeves, CDRH, HFZ-440, 7/30/97, 594-1293
Prepared by Peter E. Maxim, CDRH, HFZ-440, 7/30/97, 594-1293
Prepared by Susan Weeks, CDRH, HFZ-440, 7/30/97 594-1293

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

DRAFT

Food and Drug Administration

[DOCKET NO. _____]

Abbott Laboratories; Premarket Approval OF IMx® PSA and AxSYM® PSA

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the supplemental application by Abbott Laboratories, Diagnostics Div., Abbott Park, IL, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of IMx® PSA and AxSYM® PSA. FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter of August 7, 1997, of the approval of the supplemental application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Peter E. Maxim,
Center for Devices and Radiological Health (HFZ-440),
Food and Drug Administration,
2098 Gaither Road,
Rockville, MD 20850,
301-594-1293.

SUPPLEMENTARY INFORMATION: On November 2, 1994, Abbott Laboratories, Abbott Park, IL 60064, submitted to CDRH a supplemental application for premarket approval of ImX® PSA and AxSYM® PSA. The devices are microparticle enzyme immunoassays (MEIA) for the quantitative measurement of Prostate Specific Antigen (PSA) in Human serum as an aid in the detection of prostate cancer when used in conjunction with digital rectal exam (DRE) in men aged 50 years or older. Prostatic biopsy is required for diagnosis of cancer.

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

On August 7, 1997, CDRH approved the supplemental application by a letter to the applicant from the Deputy Director of Clinical and Review Policy, of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity For Administrative Review

Section 515(d)(3) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under 21 CFR part 12 of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 21 CFR 10.33(b). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny

the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h) (21 U.S.C. 360e(d))), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Joy C. Sonsalla
Sr. Regulatory Specialist
Abbott Diagnostics Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, IL 60064

AUG - 7 1997

P910007/Supplement 4
Abbott IMx® and AxSYM® PSA assays
Filed: November 2, 1994
Amended: Nov 15, 1994, Dec 1, 1994, Nov 22, 1995, Feb 16, 1996, Sep 3, 1996, Nov 4, 1996, May 23, 1997 and August 1, 1997

Dear Ms. Sonsalla:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) supplement, which requested approval for the addition of a new Intended Use and is indicated for the quantitative measurement of Prostate Specific Antigen (PSA) in: 1) Human serum as an adjunctive test used as an aid in the management of prostate cancer patients; 2) Human serum as an aid in the detection of prostate cancer when used in conjunction with digital rectal exam (DRE) in men aged 50 years or older. Prostatic biopsy is required for diagnosis of cancer. Based upon the information submitted, the PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device as modified by your PMA supplement upon receipt of this letter.

The sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109.

Expiration dating for this device has been established and approved at 12 months. This is to advise you that the protocol used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

Failure to comply with the conditions of approval as attached invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

You are reminded that as soon as possible, and before commercial

distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have questions concerning this approval order, please contact Dr. Peter Maxim at (301) 594-1293.

Sincerely yours,

Kimber Richter

Kimber Richter, M. D.
Deputy Director for Clinical and Review Policy
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Summary of Safety and Effectiveness

I. General Information

Generic Name: Microparticle Enzyme Immunoassay (MEIA) for the Quantitative Measurement of Prostate Specific Antigen (PSA) in Human Serum

Trade Names: Abbott IMx® PSA
Abbott AxSYM® PSA

Applicant's Name and Address: Abbott Laboratories
Diagnostics Division
Abbott Park, IL
60064-3500

Premarket Approval Supplemental Application: P910007/S4

Date of Panel Recommendation:

Pursuant to section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not the subject of an FDA Immunology Devices Advisory Panel meeting because the information in the PMA supplement substantially duplicates information previously reviewed by this panel.

Date of Notice of Approval of Application: August 7, 1997

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II. Indications for Use

The Abbott IMx® PSA assay and the Abbott AxSYM® PSA assay were originally indicated for the quantitative measurement of Prostate Specific Antigen (PSA) in human serum as an adjunctive test to aid in the management of prostate cancer patients. The Abbott IMx PSA assay was approved on September 25, 1991 (P910007) and the AxSYM PSA assay was approved on March 29, 1995 (P910007 supplement 2). Further information may be obtained in writing from Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, room 1-23, Rockville, MD 20857, Docket number 91M-0411.

The Abbott IMx® PSA assay and the Abbott AxSYM® PSA assay are indicated for the quantitative measurement of Prostate Specific Antigen (PSA) in: 1) Human serum as an adjunctive test used as an aid in the management of prostate cancer patients; 2) Human serum as an aid in the detection of prostate cancer when used in conjunction with digital rectal exam (DRE) in men aged 50 years or older. Prostatic biopsy is required for diagnosis of cancer.

III. Background

Prostate cancer is the most common type of cancer found in men in the United States, with an incidence of approximately one case in every 10 men (1). The diagnosis of carcinoma of the prostate is hindered by the lack of symptoms in men with localized tumors. The traditional method for detection of prostate cancer is the digital rectal examination (DRE). However, only 30% to 40% of cancers detected by DRE screening are expected to be confined to the prostate (2,3).

The finding of locally advanced prostate cancer in patients may be due to the inability of DRE to detect tumors of small volume that are most likely to be confined to the prostate (4). Since patients with small size tumors are believed to have the best prognosis, it can be concluded that DRE has limited sensitivity in detecting those tumors with the greatest potential for cure (5). In a 1990 publication by Cooner, et al., data were presented regarding the clinical use of other diagnostic modalities such as prostate ultrasonography and serum prostate specific antigen (PSA) for detection of prostate cancer. This study found that there was a significant increase in the detection of cancer when the DRE and PSA tests were abnormal (6).

Other studies have shown that the measurement of serum PSA concentrations offers advantages in the detection of prostate cancer (7,8). In several recent studies of healthy men 50 or more years old, serum PSA levels in conjunction with digital rectal examination had the greatest ability to detect prostate cancer (7,8). These studies concluded that serum PSA measurement is a useful addition to rectal examination and ultrasonography in the detection of prostate cancer in men aged 50 and older (7,8). Elevated serum PSA concentration can only suggest the presence of prostate cancer. Prostatic biopsy is required for definitive diagnosis of cancer.

Prostate Specific Antigen (PSA), first described in 1979 by Wang, et al., is a secretion of prostate epithelium and is also produced by prostate cancer cells. PSA was characterized as a glycoprotein monomer of 33-34,000 molecular weight with protease activity (9,10). More recently the amino acid sequence of the antigen has been reported (11) and the gene for PSA has been cloned (12). Development of an enzyme immunoassay by Kuriyama, et al., made it possible to detect low concentrations of PSA in the blood of patients with malignant and benign prostate disease and a significant proportion of normal males (13). This study also reported an exclusive association of PSA with prostate tissue, a finding confirmed by immunocytochemical analysis and subsequent clinical studies (14-17).

PSA testing can have significant value in detecting metastatic or persistent disease in patients following surgical or medical treatment of prostate cancer (16,18). Persistent elevation of PSA following treatment or increase in a pretreatment PSA level is indicative of recurrent or residual disease (14,19,25). PSA testing is an adjunctive test in the management of prostate cancer patients (17,20-26).

IV. Contraindications

There are no known contraindications for the IMx® and AxSYM® PSA Test.

V. Warnings and Precautions

Warnings and precautions for use of the devices are stated in the attached product labeling (Attachment A).

VI. Device Description

The devices are in vitro diagnostic devices to determine the PSA concentration in human serum. They utilize enzyme immunoassay technology and are performed on automated analyzers. Microparticle bound anti-PSA antibody captures the analyte in serum containing PSA. Detection of the bound PSA is visualized with a second anti-PSA antibody conjugated with an enzyme label and a fluorescent labeled enzyme substrate. The amount of bound PSA is proportional with the amount of fluorescent label produced in the assay. The sample PSA concentration is calculated from a calibration curve determined using calibrators of known PSA concentration and the amount of fluorescent label produced by these calibrators.

The assay procedure occurs in the following sequence:

1. The sample (calibrator, control or specimen) is manually (non-precision) added to the sample well of an reaction cell. All the following steps are automatically performed by the instrument.
2. The sample, Assay Diluent, and Anti-PSA Coated Microparticles are added to the incubation well of the reaction cell and allowed to incubate. The PSA in the sample binds to the Anti-PSA Coated Microparticles forming an antibody-antigen complex.

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3. An aliquot of this reaction mixture which contains the antibody-antigen complex bound to the microparticles is transferred to the reaction cell's glass fiber matrix. The microparticles bind irreversibly to the glass fiber matrix.
4. The matrix is washed with Diluent Buffer to remove unbound materials.
5. The Anti-PSA: Alkaline Phosphatase Conjugate is dispensed onto the matrix and binds the antibody-antigen complex.
6. The substrate, is added to the matrix and, in the presence of the alkaline phosphatase conjugate, a fluorescent product, develops. The rate of fluorescent product formation is measured by the IMx® or AxSYM® instruments.

The instrument prepares and stores a calibration curve using the concentrations of the calibrators versus their respective rates of fluorescent product formation. On subsequent assay runs a single calibrator (Mode 1) is included to adjust the stored calibration curve. The PSA concentrations of controls and specimens are then determined from this calibration curve.

VII. Alternative Practices and Procedures

Alternative practices and/or procedures for detection of prostate cancer patients include digital rectal exam, ultrasound and biopsy.
Alternative practices and procedures for management of prostate cancer patients include serial determinations of certain enzymes (e.g. prostatic acid phosphatase, alkaline phosphatase, total acid phosphatase, or total alkaline phosphatase), imaging (e.g. bone scans, whole body scans, or lymphangiography, X-rays, or ultrasound), biopsy, and digital rectal examination.

VIII. Marketing History

The Abbott IMx® PSA assay has been marketed in the US and Europe since 1991 for management of prostate cancer patients. The Abbott AxSYM® PSA assay has been marketed in Europe since 1994 and in the US since 1995 for management of prostate cancer patients. Neither device has been withdrawn from marketing in any country for any reason relating to the safety and effectiveness of the devices.

IX. Potential Adverse Effects of the Device on Health

Since elevations of PSA occur in benign prostatic disorders and low concentrations do not always mean absence of disease, assessment of patient status should not be based solely on a PSA results. The following adverse clinical events may occur:

1. A falsely low result could lead to a medical decision depriving the patient of potentially beneficial treatment.

2. A falsely elevated result could lead to a medical decision causing a patient

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to undergo needless treatment.

X. Summary of Studies

A. Non-clinical Studies

Because approval was requested only for an additional intended use and did not involve any changes in the reagents or test procedures, limited data were necessary to characterize the assays for the new Intended Use. The data is found in the labeling.

B. Clinical Study

Clinical studies were conducted at nine clinical sites. These sites conducted prostate cancer screening studies during the period of September, 1994 through September, 1995.

The clinical study was retrospective in design and was designed to confirm the hypothesis that elevated PSA values as measured by both devices aid in the detection of prostate cancer when used in conjunction with digital rectal exam (DRE) in men age 50 years or older compared to detection by DRE only.

Inclusion criteria for the study included men aged 50 and older with no personal history of prostate cancer. Exclusion criteria include men with previously diagnosed prostatitis or urinary tract infections, men younger than 50 years of age, and men with a history of prostate cancer.

A total of 5,408 subjects were enrolled in the study. Based on the exclusion criteria outlined in the clinical protocol, 838 subjects were excluded. The final results are based on an analysis of 4,570 eligible subjects. All eligible men were examined by DRE, had a serum sample taken for PSA determination using the IMx® PSA assay, and had a personal history recorded. Serum samples from a subset of the eligible men (930) were additionally tested using the AxSYM® PSA assay.

1. Distribution of PSA levels and DRE results

For all subjects tested using the IMx® assay, 12.3 per cent (561/4570) had serum PSA levels > 4.0 ng PSA/mL, 8.6 per cent (391/4570) had suspicious findings on DRE and 18.1 per cent (827/4570) had abnormal results on either or both PSA test or DRE. Three thousand seven hundred and forty-three subjects (81.9 per cent) had normal results for both the IMx® PSA test and DRE. These subjects exited the study. A small percentage of the population tested had results that overlapped: only 125 men

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(2.7 per cent) had abnormal findings by both methods, compared to 436 (9.5 per cent) with elevated PSA levels alone and 266 (5.8 per cent) with suspicious DRE findings alone.

For all subjects tested using the AxSYM® PSA assay, 7.2 per cent (67/930) had serum PSA levels > 4 ng/mL, 4.0 per cent (37/930) had suspicious DRE results, and 9.8 per cent (91/930) had abnormal results on either or both the AxSYM® PSA test or DRE. Eight hundred and thirty nine men (90.2 per cent) had negative results on both the AxSYM® PSA test and DRE. For the 930 men tested using the AxSYM® PSA assay and the IMx® PSA assay, the Pearson correlation coefficient between PSA values was 0.997. The slope (± 1 standard error) of the best fit line was 0.976 ± 0.002. The y-intercept (± 1 standard error) was 0.091 ± 0.011. When characterizing the IMx® PSA and AxSYM® PSA result as positive (> 4 ng/mL) or negative (< 4 ng/mL) and comparing the relative agreement between assays for these categories, there was 99.1 per cent agreement between assays. The agreement by chance between assays for these categories was 87%. The probability of agreement by chance between assay categories was less than 0.0001. This data supports the hypothesis of agreement between assay results for positive and negative categories.

2. Patient Follow-up

Of the 827 subjects who had suspicious findings on one or both of the IMx® PSA test or DRE, 405 (49.0 per cent) underwent biopsy. Of the patients biopsied, 283 had an elevated PSA level and 214 had a suspicious DRE. The mean subject age± 1 standard deviation for the biopsied group was 66.0± 7.5 years compared to 67.6 ± 8.1 years for the non-biopsied group.

There were 422 subjects that exited the study even though one or both of the IMx® PSA test or DRE was abnormal. Reasons for not having a follow-up biopsy include: results from other diagnostic tests (*i.e.* Ultrasound) or clinical observations, demographic data errors (address, phone number), refused to have follow-up, insurance concerns and others.

Of the 91 subjects who had suspicious results on one or both of the AxSYM® PSA test or DRE, 43 (45.3 per cent) underwent biopsy. Of the biopsied subjects, 33 had elevated AxSYM® PSA tests and 16 had a suspicious DRE. Four of 839 men without suspicious results also underwent biopsy, all of whom had a negative biopsy.

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3. Detection Rate

Of the 405 subjects initially identified by DRE and/or the IMx® PSA assay who underwent biopsy, 133 cancers were detected. The cancer detection rate was determined by multiplying the number of subjects with suspicious results by the percent of cancers detected from the biopsied subjects and then dividing by the number of subjects enrolled in the study. This assumes that the cancer detection rate would remain constant if all men with suspicious findings were biopsied, rather than the 50 per cent, approximately, who actually were biopsied. The overall cancer detection rate was 5.94 per cent for either test positive, 1.46 per cent for both tests positive, 4.94 per cent for PSA positive alone and 2.72 per cent for DRE positive alone.

Of the 91 subjects initially identified by DRE and/or the AxSYM® PSA assay who underwent biopsy, 15 cancers were detected. The overall cancer detection rate for both DRE and AxSYM® PSA test was 0.98 per cent (compared with 1.46 per cent for both DRE and the IMx® PSA assay). The overall cancer detection rate was 3.4 per cent for either DRE or AxSYM® test positive (compared with 5.94 per cent for either DRE or IMx® test positive).

4. Positive Predictive Value

The positive predictive value was 40.3 per cent for elevated levels in the IMx® PSA (>4.0 ng PSA/mL) and 31.8 per cent for a suspicious DRE. When the IMx® PSA levels were > 4.0 ng PSA/mL but the DRE was not suspicious, the positive predictive value was 34.0 per cent.. When the DRE was suspicious but the IMx® PSA level was $\leq$ 4.0 ng PSA/mL, the positive predictive value was 15.6 per cent . When both were suspicious for cancer, the positive predictive value was 53.3 per cent.

The positive predictive value for elevated levels of the IMx® PSA and suspicious DRE was significantly greater than that for suspicious DRE (p-value < 0.0001, Binomial Test). The positive predictive value for elevated levels of the IMx® PSA and normal DRE was significantly greater than 15 per cent (p-value < 0.0001, Binomial Test).

A logistic regression based on the biopsied subjects showed that IMx® PSA levels > 4.0 ng PSA/mL was a significant predictor of prostate cancer (p-value < 0.0001, Wald Chi-Square Test). DRE was a significant predictor of prostate cancer (p-value = 0.0054,

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Wald Chi-Square Test). Age was also a significant predictor of prostate cancer (p-value = 0.029, Wald Chi-Square Test). The odds ratio (and 95 per cent confidence intervals) for the IMx® PSA was 5.57 (2.92,10.63), for DRE it was 2.07 (1.24, 3.46) and for age it was 1.03 (1.00, 1.07).

XI. Conclusions drawn from the studies

The primary objective of this multiple site, retrospective clinical study was to confirm the hypothesis that elevated PSA values as measured by the Abbott IMx® and AxSYM® PSA assay aid in the detection of prostate cancer when used in conjunction with DRE.

The previously presented clinical data supports the clinical utility of the Abbott IMx® and AxSYM® PSA assay as an aid in the detection of prostate cancer when use in conjunction with digital rectal exam (DRE) in men aged 50 years or older.

XII. Panel Recommendation

Pursuant to section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to the Immunology Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA supplement substantially duplicates information previously reviewed by this panel.

XIII. CDRH Action on the Application

CDRH issued an approval order for the applicant's PMA for the Abbott IMx® PSA and Abbott AxSYM® PSA to Abbott Laboratories on August 7, 1997.

XIV. Approval Specifications

Directions for use: See labeling.

Conditions of Approval: CDRH approval of this PMA supplement is subject to full compliance with the conditions described in the approval order.

References for the Summary of Safety and Effectiveness

1. CA-A Cancer Journal for Clinicians. 1996. American Cancer Society, Inc. 46:5.

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TUMOR MARKERS

IM® SYSTEM

PSA

Note Changes Highlighted

Customer Support Center (USA)
1-800-527-1869

66-9950/R9

ABBOTT LABORATORIES
Diagnostics Division
Abbott Park, IL 60064

August, 1997

Printed in U.S.A.
List No. 2245

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CAUTION: United States Federal law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and use is restricted to, by or on the order of a physician.

WARNING: The concentration of PSA in a given specimen, determined with assays from different manufacturers, can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the PSA assay used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining PSA levels serially is changed, additional sequential testing should be carried out. Prior to changing assays, the laboratory MUST confirm baseline values for patients being serially monitored.

Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies. These specimens should not be assayed with the IMx® PSA assay.

Refer to the **LIMITATIONS OF THE PROCEDURE** section in this assay package insert.

NAME

PSA: Prostate Specific Antigen

INTENDED USE

The Abbott IMx PSA assay is a Microparticle Enzyme Immunoassay (MEIA) for the quantitative measurement of Prostate Specific Antigen (PSA) in human serum:

1. as an aid in the detection of prostate cancer when used in conjunction with digital rectal exam (DRE) in men aged 50 years or older. Prostatic biopsy is required for diagnosis of cancer.
2. as an adjunctive test used as an aid in the management of prostate cancer patients.

SUMMARY AND EXPLANATION OF THE TEST

Prostate cancer is the most common type of cancer found in men in the United States, with an incidence of approximately one case in every 10 men.[1] Early diagnosis of carcinoma of the prostate is hindered by the lack of symptoms in men with localized tumors. Therefore, early detection requires a simple, safe, and inexpensive test for the disease in asymptomatic men. The traditional method for detection of prostate cancer is the digital rectal examination (DRE). However, only 30% to 40% of cancers detected by DRE screening are expected to be confined to the prostate. In January, 1992, the American Urological Association (AUA) endorsed annual examination for early detection of prostate cancer with DRE and PSA beginning at age 50.[2] This was reaffirmed by the American Cancer Society (ACS) in November, 1992.[3]

The frequent finding of locally advanced prostate cancer in screened patients may be due to the inability of DRE to detect tumors of small volume that are most likely to be confined to the prostate.[4] Since patients with small size tumors are believed to have the best prognosis, it can be concluded that DRE has limited sensitivity in detecting those tumors with the greatest potential for cure.[5] In a 1990 publication by Cooner, *et al.*, data was presented regarding the clinical use of other diagnostic modalities such as prostate ultrasonography and serum prostate specific antigen (PSA) for early detection of prostate cancer. This study found that there was a significant increase in predictability for cancer when the DRE and PSA tests were abnormal.[6]

Several other studies have shown that the measurement of serum PSA concentrations offers several advantages in the early detection of prostate cancer. The procedure is more acceptable to patients, the result is objective and quantitative and is independent of the examiner's skill. In several recent studies of healthy men 50 or more years old, serum PSA levels had the greatest ability to predict prostate cancer. These studies concluded that not only is serum PSA measurement a useful addition to rectal examination and ultrasonography in the detection of prostate cancer, but that it is also the most accurate of the three tests for this purpose.[7,8]

Elevated serum PSA concentration can only suggest the presence of prostate cancer. Prostatic biopsy is required for diagnosis of cancer.

Prostate Specific Antigen (PSA), first described in 1979 by Wang, *et al.*, is a secretion of prostate epithelium and is also produced by prostate cancer cells. PSA was characterized as a glycoprotein monomer of 33-34,000 molecular weight with protease activity.[9,10] More recently the amino acid sequence of the antigen has been reported[11] and the gene for PSA has been cloned.[12] Development of an enzyme immunoassay by Kuriyama, *et al.*, made it possible to detect low concentrations of PSA in the blood of patients with malignant and benign prostate disease and a significant proportion of normal males.[13] This study also reported an exclusive association of PSA with prostate tissue, a finding which was confirmed by immunocytochemical analysis and subsequent clinical studies.[14-17]

PSA testing can have significant value in detecting metastatic or persistent disease in patients following surgical or medical treatment of prostate cancer.[16,18] Persistent elevation of PSA following treatment or increase in a post-treatment PSA level is indicative of recurrent or residual disease.[14,19,25] PSA testing is widely accepted as an adjunctive test in the management of prostate cancer patients.[17,20-26]

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

The IMx PSA assay is based on the Microparticle Enzyme Immunoassay (MEIA) technology. The IMx PSA reagents and sample are added to the reaction cell in the following sequence:

- The probe/electrode assembly delivers the sample, Anti-PSA Coated Microparticles and Assay Diluent to the incubation well of the reaction cell. During the incubation of this reaction mixture, the PSA in the sample binds to the Anti-PSA Coated Microparticles forming an antibody-antigen complex.
- An aliquot of the reaction mixture is transferred to the glass fiber matrix. The microparticles bind irreversibly to the glass fiber matrix.
- The matrix is washed to remove unbound materials.
- The Anti-PSA:Alkaline Phosphatase Conjugate is dispensed onto the matrix and binds to the antibody-antigen complex.
- The matrix is washed to remove unbound materials.

- The substrate, 4-Methylumbelliferyl Phosphate, is added to the matrix and the fluorescent product is measured by the MEIA optical assembly.

For further information, refer to your IMx® System Operation Manual, Section 3.

REAGENTS

REAGENT PACK

IMx PSA Reagent Pack, 100 Tests (No. 2245-20)*

1. 1 Bottle (5.8 mL) Anti-PSA (Mouse, Monoclonal) Coated Microparticles in TRIS buffer. Preservative: Sodium Azide.
2. 1 Bottle (9.8 mL) Anti-PSA (Goat):Alkaline Phosphatase Conjugate in TRIS buffer with protein stabilizers. Minimum Concentration: 0.1 µg/mL. Preservative: Antimicrobial Agents.
3. 1 Bottle (10 mL) 4-Methylumbelliferyl Phosphate, 1.2 mM in AMP buffer. Preservative: Sodium Azide.
4. 1 Bottle (14 mL) Assay Diluent, buffered calf serum with protein stabilizers. Preservatives: Sodium Azide and Antimicrobial Agents.

IMx PSA MODE 1 Calibrator

1 Bottle (4 mL) MODE 1 Calibrator (C). *Concentration*: 10 ng/mL PSA (Human), nonreactive for anti-HIV-1/HIV-2 and anti-HCV and nonreactive for HBsAg, in TRIS buffer with protein stabilizers. Preservatives: Sodium Azide and Antimicrobial Agents.

*No. 2245-66 includes an IMx PSA Reagent Pack (100 tests), IMx PSA MODE 1 Calibrator and reaction cells (100 each). No. 2245-20 includes these items for international shipments.

CALIBRATORS

IMx PSA Calibrators (No. 2245-01)/PSA Calibrators (No. 9C04-01)

6 Bottles (4 mL each) of PSA Calibrators are prepared with PSA (Human), nonreactive for anti-HIV-1/HIV-2 and anti-HCV and nonreactive for HBsAg, in TRIS buffer with protein stabilizers to yield the following concentrations:

Bottle	PSA Concentration (ng/mL)
A	0
B	2
C	10
D	30
E	60
F	100

Preservatives: Sodium Azide and Antimicrobial Agents.

CONTROLS

IMx PSA Controls (No. 2245-10)/PSA Controls (No. 9C04-10)

3 Bottles (8 mL each) of PSA Controls are prepared with PSA (Human), nonreactive for anti-HIV-1/HIV-2 and anti-HCV and nonreactive for HBsAg, in TRIS buffer with protein stabilizers to yield the following concentration ranges:

Bottle	PSA Concentration (ng/mL)	Range (ng/mL)
L	4	3 - 5
M	15	12 - 18
H	45	36 - 54

Preservatives: Sodium Azide and Antimicrobial Agents.

SPECIMEN DILUENT

IMx PSA Specimen Diluent (No. 2245-50)

1 Bottle (100 mL) PSA Specimen Diluent, buffered goat serum. Preservatives: Sodium Azide and Antimicrobial Agents.

WARNINGS AND PRECAUTIONS

For *In Vitro* Diagnostic Use.

CAUTION: This product contains human sourced and/or potentially infectious components. For a specific listing, refer to the **REAGENTS** section of this package insert. Donors have been tested and found to be nonreactive for antibodies to HIV-1/HIV-2 and HCV and nonreactive for HBsAg. No known test method can offer complete assurance that products derived from human sources or inactivated microorganisms will not transmit infection. Therefore, all human sourced materials should be considered potentially infectious. It is recommended that these reagents and human specimens be handled in accordance with the OSHA Standard on Bloodborne Pathogens.[27] Biosafety Level 2[28] or other appropriate biosafety practices[29,30] should be used for materials that contain or are suspected of containing infectious agents.

The safety and handling precautions and limitations for the reagent pack, calibrators, controls, and patient samples are described in your IMx System Operation Manual, Section 8.

Some components of this product contain Sodium Azide. For a specific listing, refer to the **REAGENTS** section of this package insert. The components Assay Diluent (2245J), MUP, MODE 1 Calibrator (2245Q), Calibrators (2245 A-F/9C04 A-F), Controls (2245 L, M, N/9C04 L, M, N) and Specimen Diluent (2245P) are classified per applicable European Economic Community (EEC) Directives as: Harmful (Xn). The following are the appropriate Risk (R) and Safety (S) phrases.

R22 Harmful if swallowed.
R32 Contact with acids liberates very toxic gas.
S2 Keep out of the reach of children.
S13 Keep away from food, drink and animal feedingstuffs.
S36 Wear suitable protective clothing.
S46 If swallowed, seek medical advice immediately and show this container or label.

STORAGE INSTRUCTIONS

The storage condition for the IMx PSA Reagent Pack, PSA Calibrators, PSA Controls and Specimen Diluent is 2-8°C. All of these reagents can be used **immediately** after removing them from the refrigerator.

INSTRUMENT PROCEDURE

The following instrument software is required to perform the assay:

- IMx System Software Module Version 6.0 or higher
- IMx Tumor Markers Assay Module Version 6.0 or higher

IMx® PSA ASSAY PARAMETERS

The following IMx PSA assay parameters have been factory set. These parameters can be printed, displayed, and edited according to the procedure in your IMx System Operation Manual, Section 6. Ensure that the assay parameters for the IMx PSA assay in the Assay Module match these parameters or edit accordingly. The assay parameters that cannot be edited are noted with an asterisk (*).

	Assay #53 IMx PSA		
	1.	DECIMAL	2
	2.	RUN DEFAULT	1
	3.	SAMPLE REP	1
	4.	CAL REP	2
	5.	M1 CAL REP	1
*	6.	CONC A	0.000
*	7.	CONC B	2.000
*	8.	CONC C	10.000
*	9.	CONC D	30.000
*	10.	CONC E	60.000
*	11.	CONC F	100.000
	12.	RESULT UNIT	1
	13.	LOW LIMIT	-9999.000
	14.	HIGH LIMIT	9999.000
	15.	C1 LOT ID	00000000
*	16.	C1 DATE	11/11/11
*	17.	C1 TIME	0:00:00
*	18.	C2 LOT ID	00000000
*	19.	C2 DATE	11/11/11
*	20.	C2 TIME	0:00:00
*	27.	LOW RANGE	0.000
*	28.	HIGH RANGE	100.000
*	29.	MIN TRACER	-9999.00
*	30.	MAX BKG	0.0
*	31.	MIN RATE	30.0
*	32.	MAX NRMSE	0.200
	34.	MAX INTRCPT	18000.0
	35.	MAX DEV	10.00
*	36.	MIN POL	-9999.00
*	37.	MIN READ	0.0
*	38.	MAX READ	35.0
	39.	MIN SPAN F-A	850.000
	40.	MAX SPAN F-A	2400.000
	41.	MIN CHECK 1	0.000
	42.	MAX CHECK 1	0.450
	43.	MIN CHECK 2	0.184
	44.	MAX CHECK 2	0.326
	45.	MIN CHECK 3	0.318
	46.	MAX CHECK 3	0.527
	47.	MIN CHECK 4	0.477
	48.	MAX CHECK 4	0.797
	49.	MIN CHECK 5	0.530
	50.	MAX CHECK 5	0.920
*	52.	DIL FACT 1	1.000
*	53.	DIL FACT 2	1.000
*	54.	DIL FACT 3	1.000
*	55.	DIL FACT 4	1.000
*	56.	DIL FACT 5	1.000
	57.	DIL DEFAULT	0
*	58.	LOW GRAY	-9999.000
*	59.	HIGH GRAY	9999.000
	60.	PRINT OPTION	0
*	61.	CUTOFF	0.000
*	87.	MX MODE1 DEV	0.350

NOTE: RESULT UNIT, assay parameter 53.12, can only be edited to "1" (ng/mL) or "17" (µg/L) and PRINT OPTION, assay parameter 53.60, can only be edited to "0" or "1." Editing to another number will result in the displayed code "103 BAD VALUE IN ASSAY FILE 12 OR 60," respectively, when the assay run is initiated. The alternate RESULT UNIT (µg/L) is available in IMx Tumor Markers Assay Module Version 7.0 (List No. 8385-07) or higher. For further information on Changing Concentration Units and Print Options, refer to your IMx System Operation Manual, Section 5.

Refer to your IMx System Operation Manual for a detailed discussion of instrument procedures.

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Only serum specimens may be used with the IMx PSA assay.

If the assay will be performed within 24 hours after collection, the specimen should be stored at 2-8°C. If testing will be delayed more than 24 hours, the specimen should be stored frozen. Mix thoroughly after thawing to ensure consistency in the results. Avoid repeated freezing and thawing.

Specimens showing particulate matter, erythrocytes, or turbidity must be clarified by centrifugation before testing.

Specimens should be obtained before patients undergo prostate manipulation procedures.

SAMPLE VOLUME

150 µL of specimen is the minimum volume required to perform the assay.

To obtain the recommended volume requirements for PSA Calibrators and Controls, hold the bottles **vertically** and dispense 4 drops into the sample well.

IMx PSA PROCEDURE

The list of required materials and the procedure to perform an IMx PSA Calibration or MODE 1 Assay can be found in your IMx System Operation Manual, Section 5.

The IMx PSA assay requires a minimum volume of 250 mL of MEIA #2 Diluent Buffer in the buffer bottle in order to properly process an assay run. Before initiating an IMx PSA assay, visually check that at least 250 mL of MEIA #2 Diluent Buffer is present. Do not add diluent buffer to the buffer bottle or switch buffer bottles during an assay run.

DILUTION INFORMATION

Specimens with a PSA value exceeding 100 ng/mL (HIGH RANGE, assay parameter 53.28) are flagged with the code ">100." To quantitate the concentration of these specimens, perform the Manual Dilution procedure.

Manual Dilution

A manual dilution can be performed by making a dilution of the specimen with the IMx PSA Specimen Diluent (No. 2245-50) before pipetting the sample into the sample well. It is desirable to perform the dilution so that the diluted specimen reads above the 2 ng/mL PSA Calibrator on the calibration curve. Example: A ten-fold dilution is prepared by adding 100 µL of specimen to 900 µL of IMx PSA Specimen Diluent. Mix thoroughly before assaying. To determine the concentration of PSA in the specimen,

multiply the concentration of the diluted sample by the dilution factor.

QUALITY CONTROL PROCEDURES

CALIBRATION

Perform an assay calibration with each new lot of IMx® PSA Reagent Pack. For an IMx PSA Calibration, run all assay-specific calibrator levels in duplicate in the first carousel positions, followed by **all** levels of controls. Controls must be processed as a means of evaluating the calibration curve. The **RESULTS** section below provides an explanation of the type of curve fit used by the IMx PSA assay and the assay-specific checks that are used to evaluate the acceptability of the curve.

Once the assay calibration is accepted and stored, all subsequent runs are tested in MODE 1 with the MODE 1 Calibrator in position 1 of the carousel.

Refer to the IMx System Operation Manual, Section 5 for:

- Setting up an assay calibration run
- When recalibration may be necessary
- System and Operator Verification
- MEIA Calibration and MEIA MODE 1 Assay Test Results Tape Explanation

QUALITY CONTROL

PSA Control values must be within the range specified in the **REAGENTS** section of this package insert. If a control value is out of its specified range, the test results may be invalid and assay recalibration may be indicated. Refer to the IMx System Operation Manual, Section 10 for a description of troubleshooting procedures.

The minimum control requirement for an IMx PSA MODE 1 Assay is **one** control on each carousel. All levels of controls should be processed at least one time during each 8 hour shift. If the quality control procedures in your laboratory require more frequent use of controls, follow those procedures.

RESULTS

The IMx PSA assay utilizes a four parameter logistic curve fit (4PLC Analysis) to generate a calibration curve. The following are assay-specific checks used to evaluate a calibration curve:

Assay Parameters	Calibrator Evaluation (AVGR)
MIN SPAN F-A	Calibrator F - Calibrator A
MAX SPAN F-A	Calibrator F - Calibrator A
MIN CHECK 1	Calibrator A/Calibrator B
MAX CHECK 1	Calibrator A/Calibrator B
MIN CHECK 2	Calibrator B/Calibrator C
MAX CHECK 2	Calibrator B/Calibrator C
MIN CHECK 3	Calibrator C/Calibrator D
MAX CHECK 3	Calibrator C/Calibrator D
MIN CHECK 4	Calibrator D/Calibrator E
MAX CHECK 4	Calibrator D/Calibrator E
MIN CHECK 5	Calibrator E/Calibrator F
MAX CHECK 5	Calibrator E/Calibrator F

The operator must confirm that the following parameters fall within the acceptable ranges:

RERR (Rate Error)	RMSE (Root Mean Square Error)
± 50	≤ 0.1

FLAGGED RESULTS

For a description of the flags that appear in the NOTE column on the test results tape, refer to your IMx System Operation Manual, Section 5.

LIMITATIONS OF THE PROCEDURE

Serum PSA concentrations should not be interpreted as absolute evidence for the presence or absence of prostate cancer. Elevated concentrations of PSA may be observed in the serum of patients with benign prostatic hyperplasia or other nonmalignant disorders as well as in prostate cancer. Furthermore, low PSA concentrations are not always indicative of the absence of cancer. The PSA value should be used in conjunction with information available from clinical evaluation and other diagnostic procedures such as DRE. Some early cases of prostate cancer will not be detected by PSA testing; the same is true for DRE. Prostatic biopsy is required for the diagnosis of cancer.

- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies.[31-33] These specimens should not be assayed with the IMx PSA assay.
- Heterophilic antibodies in serum have the potential to cause interference in immunoassay systems.[34,35] Infrequently, PSA levels may appear elevated due to heterophilic antibodies present in the patient's serum or to nonspecific protein binding. If the PSA level is inconsistent with clinical evidence, additional PSA testing is suggested to confirm the result.
- The concentration of PSA in a given specimen, determined with assays from different manufacturers, can vary due to differences in assay methods, calibration, and reagent specificity.[25,36] PSA in serum and in seminal fluid may exist in different forms. Quality control samples may be produced by introducing seminal fluid PSA into a human serum matrix. The concentration of PSA in these controls, determined with assays from different manufacturers, can vary due to differences in assay methods, calibration, reagent specificity and the form of PSA that is present; therefore, it is important to use assay-specific values to evaluate quality control results.
- Specimens obtained from patients immediately following digital rectal examination show no clinically significant increases in PSA levels.[37] However, prostatic massage, ultrasonography and needle biopsy may cause clinically significant elevations.[38] Hormonal therapy may affect PSA expression; therefore, a low PSA level after any treatment that includes hormonal therapy may not adequately reflect the presence of residual or recurrent disease.[39]

EXPECTED VALUES IN DETECTION OF PROSTATE CANCER

A retrospective study was conducted at nine clinical sites to demonstrate the usefulness of PSA in the detection of prostate cancer when used in conjunction with DRE. A total of 4,570 men 50 years of age or older participated in the study. A distribution of the initial testing results is presented in Table 1.

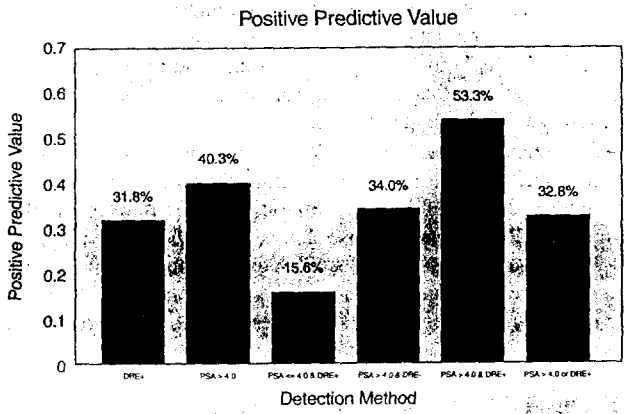
Table 1
Distribution of Results from Initial Testing

	PSA > 4.0	PSA ≤ 4.0	Total
DRE+	125	266	391
%	2.7%	5.8%	8.6%
DRE-	436	3,743	4,179
%	9.5%	81.9%	91.4%
Total	561	4,009	4,570
%	12.3%	87.7%	100%

Note: 827 Patients Tested Positive by DRE and/or PSA

DRE - Digital Rectal Examination
Key: + Suspicious for Cancer
- Not Suspicious for Cancer

The study demonstrated that PSA levels, were more predictive of prostate cancer than DRE alone. The positive predictive value was 40.3% for elevated levels of PSA (>4.0 ng PSA/mL) and 31.8% for a suspicious DRE. When PSA levels were >4.0 ng PSA/mL but the DRE was not suspicious, the positive predictive value was 34.0%. When the DRE was suspicious but the PSA level was ≤ 4.0 ng PSA/mL, the positive predictive value was 15.6%. When both tests were suspicious for cancer, the positive predictive value was 53.3%. This is presented graphically.



Of the 4,570 subjects studied, 405 were biopsied based on an elevated PSA or a suspicious DRE. The percentage of biopsied patients with cancer corresponding to PSA and DRE results are shown in Table 2.

Table 2
Positive Predictive Values

Detection Method	Positive Predictive Value%*	Number of Biopsied Subjects with Cancer
DRE+	31.8% (25.5% - 38.0%)	68/214
PSA > 4.0	40.3% (34.6% - 46.0%)	114/283
PSA ≤ 4.0 DRE+	15.6% (9.1% - 22.0%)	19/122
PSA >4.0 DRE-	34.0% (27.3% - 40.8%)	65/191
PSA >4.0 DRE+	53.3% (43.1% - 63.5%)	49/92
PSA >4.0 or DRE+	32.8% (28.3% - 37.4%)	133/405

* 95% Confidence Interval (Lower Limit - Upper Limit)

Of the 405 subjects who underwent biopsy, 133 cancers were detected. The overall cancer detection rate was 5.94% for either test, 1.46% for both tests, 4.94% for PSA alone and 2.72% for DRE alone. These results are shown in Table 3.

Table 3
Cancer Detection Rate

Detection Method	Cancer Detection Rate	Calculation*
DRE+	2.72%	68*(391/214) / 4570
PSA >4.0	4.94%	114*(561/283) / 4570
PSA >4.0 & DRE+	1.46%	49*(125/92) / 4570
PSA >4.0 or DRE+	5.94%	133*(827/405) / 4570

*Cancer Detection Rate = Number of Cancers * (Num. of Test Positive/Num. of Biopsy) / Number of Screened Patients

Serum PSA concentrations, regardless of the value, should not be interpreted as definitive evidence for the presence or absence of prostate cancer. In addition, PSA testing should be done in conjunction with DRE, because PSA and DRE together detected the greatest number of cancers. Prostatic biopsy is required for the diagnosis of cancer.

EXPECTED VALUES FOR PROGNOSIS AND MANAGEMENT

The distribution of PSA values determined in 2984 specimens is shown in the following table:

Distribution of PSA Values

	Number of Subjects	Percent (%) 0-4.0 ng/mL	4.1-10 ng/mL	10.1-30 ng/mL	30.1-60 ng/mL	>60 ng/mL
Healthy Subjects						
Males >40 yrs	394	98.7	0.8	0.5	0.0	0.0
Males <40 yrs	309	99.7	0.3	0.0	0.0	0.0
Females	50	100.0	0.0	0.0	0.0	0.0
Malignant Diseases						
Prostate						
Stage A	151	61.6	21.2	13.9	2.6	0.7
Stage B	224	47.8	25.9	16.5	4.9	4.9
Stage C	272	31.6	16.9	27.2	11.0	13.2
Stage D	397	20.9	10.8	14.6	7.8	45.8
Gastrointestinal	166	83.1	13.3	1.8	0.0	1.8
Pulmonary	119	94.1	5.0	0.8	0.0	0.0
Genitourinary	133	88.0	6.0	4.5	1.5	0.0
Nonmalignant Diseases						
BPH	337	71.5	16.9	9.2	1.5	0.9
Prostatitis	59	76.3	11.9	10.2	0.0	1.7
Genitourinary	124	93.6	4.0	2.4	0.0	0.0
Renal	128	85.2	8.6	6.2	0.0	0.0
Hepatic	121	92.6	6.6	0.8	0.0	0.0

In this study, 99% of the specimens from normal males (n=703) had values of 4.0 ng/mL or less.

It is recommended that each laboratory establish its own expected reference range for the population of interest.

The distribution table is derived primarily from monitored carcinoma patients representing both active (clinical evidence of disease progression) and inactive (no clinical evidence of disease progression) disease states. When changing PSA assay methods, in the course of monitoring a patient, additional sequential testing should be carried out to confirm baseline values.

SPECIFIC PERFORMANCE CHARACTERISTICS

PRECISION

Assay reproducibility was determined by assaying 6 samples in replicates of 3 in 10 independent runs at 6 laboratories (n=180 for each sample). The coefficient of variation (%CV) for between run and between lab were determined from the components of variance[40] which gives a statistical estimate of the variation of replicates of one for multiple assay runs. Within run %CVs were calculated for replicates of 3.

Reproducibility of IMx PSA Assay

Sample	Mean Value (ng/mL)	Within Run CV (%)	Between Run CV (%)	Between Lab CV (%)
1	1.41	3.7	5.6	6.5
2	4.59	3.5	4.7	5.0
3	15.58	3.3	4.5	5.0
4	35.09	3.0	4.9	5.3
5	60.23	3.1	5.3	5.7
6 (1:10)	397.89	2.9	5.9	7.1

RECOVERY

Known amounts of serum PSA were added to normal human serum and prostate cancer serum samples. The concentration of PSA was determined using the IMx® PSA assay and the resulting percent recovery was calculated.

Recovery of PSA

Sample	Endogenous Level (ng/mL)	PSA Added (ng/mL)	Value Obtained (ng/mL)	Percent Recovery*
Normal Male Serum	0.44	6.34	6.21	91
		28.55	26.98	93
Prostate Cancer Serum	18.72	6.34	25.26	103
		28.55	47.60	101

$$\%\ \text{Recovery} = \frac{\text{PSA Value Obtained (ng/mL)} - \text{Endogenous Level (ng/mL)}}{\text{PSA Added (ng/mL)}} \times 100$$

SENSITIVITY

The sensitivity of the IMx PSA assay was calculated to be better than 0.1 ng PSA/mL. This sensitivity is defined as the concentration at two standard deviations above the PSA Calibrator A (0 ng/mL), representing the lowest measurable concentration of PSA that can be distinguished from zero.

SPECIFICITY

The specificity of the IMx PSA assay was analyzed by testing sera containing the compounds listed in the following table. These compounds did not show interference in the IMx PSA assay at the levels indicated.

INTERFERING SUBSTANCES

Test Compound	Test Concentration
Bilirubin	25 mg/dL
Hemoglobin	600 mg/dL
IgG	250-2900 mg/dL
Prostatic Acid Phosphatase	1000 ng/mL
Protein	3-13 g/dL
Triglycerides	3000 mg/dL

CHEMOTHERAPEUTIC AGENTS

Test Compound	Test Concentration
Cyclophosphamide	700 µg/mL
Diethylstilbestrol	2 µg/mL
Doxorubicin-HCl	16 µg/mL
Estramustine phosphate	200 µg/mL
Flutamide	10 µg/mL
Goserelin Acetate	100 ng/mL
Lupron®	100 µg/mL
Megestrol acetate	90 µg/mL
Methotrexate	30 µg/mL

CARRYOVER

No significant carryover (less than 0.0003%) was detected when a sample containing 61,100 ng/mL of PSA was assayed.

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Abbott
AXSYM® SYSTEM

TUMOR MARKERS

PSA

Note Changes Highlighted

Customer Support Center (USA)
1-800-527-1869

ABBOTT LABORATORIES
Diagnostics Division
Abbott Park, IL 60064

August, 1997

List No. 7A49
Printed in U.S.A.

30

CAUTION: United States Federal law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory, and use is restricted to, by or on the order of a physician.

WARNING:

The concentration of PSA in a given specimen, determined with assays from different manufacturers, can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the PSA assay used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining PSA levels serially is changed, additional sequential testing should be carried out. Prior to changing assays, the laboratory MUST confirm baseline values for patients being serially monitored.

Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies. These specimens should not be assayed with the AxSYM® PSA assay. Refer to the **LIMITATIONS OF THE PROCEDURE** section in this assay package insert.

NAME:

PSA: Prostate Specific Antigen

INTENDED USE

The Abbott AxSYM PSA assay is a Microparticle Enzyme Immunoassay (MEIA) for the quantitative measurement of Prostate Specific Antigen (PSA) in human serum:

1. as an aid in the detection of prostate cancer when used in conjunction with digital rectal exam (DRE) in men aged 50 years or older. Prostatic biopsy is required for diagnosis of cancer.
2. as an adjunctive test used as an aid in the management of prostate cancer patients.

SUMMARY AND EXPLANATION OF THE TEST

Prostate cancer is the most common type of cancer found in men in the United States, with an incidence of approximately one case in every 10 men.[1] Early diagnosis of carcinoma of the prostate is hindered by the lack of symptoms in men with localized tumors. Therefore, early detection requires a simple, safe, and inexpensive test for the disease in asymptomatic men. The traditional method for detection of prostate cancer is the digital rectal examination (DRE). However, only 30% to 40% of cancers detected by DRE screening are expected to be confined to the prostate.[2] In January, 1992, the American Urological Association (AUA) endorsed annual examination for early detection of prostate cancer with DRE and PSA beginning at age 50.[3] This was reaffirmed by the American Cancer Society (ACS) in November, 1992.[3]

The frequent finding of locally advanced prostate cancer in screened patients may be due to the inability of DRE to detect tumors of small volume that are most likely to be confined to the prostate.[4] Since patients with small size tumors are believed to have the best prognosis, it can be concluded that DRE has limited sensitivity in detecting those tumors with the greatest potential for cure.[2] In a 1990 publication by Cooner, *et al.*, data was presented regarding the clinical use of other diagnostic modalities such as prostate ultrasonography and serum prostate specific antigen (PSA) for early detection of prostate cancer. This study found that there was a significant increase in predictability for cancer when the DRE and PSA tests were abnormal.[5]

Several other studies have shown that the measurement of serum PSA concentrations offers several advantages in the early detection of prostate cancer. The procedure is more acceptable to patients, the result is objective and quantitative, and is independent of the examiner's skill. In several recent studies of healthy men 50 or more years old, serum PSA levels had the greatest ability to predict prostate cancer. These studies concluded that not only is serum PSA measurement a useful addition to rectal examination and ultrasonography in the detection of prostate cancer, but that it is also the most accurate of the three tests for this purpose.[7,8]

Elevated serum PSA concentration can only suggest the presence of prostate cancer. Prostatic biopsy is required for diagnosis of cancer.

Prostate Specific Antigen (PSA), first described in 1979 by Wang, *et al.*, is a secretion of prostatic epithelium and is also produced by prostatic cancer cells.[9] PSA is characterized as a glycoprotein (molecular weight 33-34,000 daltons) with protease activity.[9,10] More recently, the amino acid sequence of the antigen has been reported[11] and the gene for PSA has been cloned.[12] Development of an enzyme immunoassay by Kuriyama, *et al.*, made it possible to detect low concentrations of PSA in the blood of patients with malignant and benign prostatic disease and in a significant proportion of normal males.[13] This study also reported the exclusive association of PSA with prostatic tissue, a finding which was confirmed by immunocytochemical analysis and subsequent clinical studies.[14,15]

PSA testing can have significant value in detecting metastatic or persistent disease in patients following surgical or medical treatment for prostatic cancer. Persistent elevation of PSA following treatment or increase in post-treatment PSA level is indicative of recurrent or residual disease.[14,16,25] PSA testing is widely accepted as an adjunctive test in the management of prostate cancer patients.[17-20,26]

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

AxSYM PSA is based on the Microparticle Enzyme Immunoassay (MEIA) technology.

The AxSYM PSA Reagents and sample are pipetted in the following sequence:

Sample and all AxSYM PSA reagents required for one test are pipetted by the Sampling Probe into various wells of a reaction vessel (RV). The RV is immediately transferred into the Processing Center. Further pipetting is done in the Processing Center by the Processing Probe.

The reactions occur in the following sequence:

- Sample, Anti-PSA Coated Microparticles and Assay Diluent are pipetted to one well of the reaction vessel. During the incubation of this reaction mixture the PSA in the specimen binds to the Anti-PSA Coated Microparticles forming an antibody-antigen complex.
- An aliquot of the reaction mixture is transferred to the matrix cell. The microparticles bind irreversibly to the glass fiber matrix.
- The matrix cell is washed to remove unbound materials.
- The Anti-PSA: Alkaline Phosphatase Conjugate is dispensed onto the matrix cell and binds to the antibody-antigen complex.
- The matrix cell is washed to remove unbound materials.
- The substrate, 4-Methylumbelliferyl Phosphate, is added to the matrix cell and the fluorescent product is measured by the MEIA optical assembly.

For further information, refer to the AxSYM System Operations Manual, Section 3.

REAGENTS

REAGENT PACK, 100 TESTS

AxSYM® PSA Reagent Pack (No. 7A49-20)*

- 1 Bottle (14.5 mL) Anti-PSA (Goat): Alkaline Phosphatase Conjugate in TRIS buffer with protein stabilizers. Minimum Concentration: 0.1 µg/mL. Preservative: Antimicrobial Agents. (Reagent Bottle 1)
- 1 Bottle (8.1 mL) Anti-PSA (Mouse, Monoclonal) Coated Microparticles in TRIS buffer. Preservative: Sodium Azide. (Reagent Bottle 2)
- 1 Bottle (17.1 mL) Assay Diluent, TRIS buffered calf serum with protein stabilizers. Preservatives: Sodium Azide and Antimicrobial Agents. (Reagent Bottle 3)

*No. 7A49-60 includes an AxSYM PSA Reagent Pack (100 tests), reaction vessels (100 each) and matrix cells (100 each). No. 7A49-20 includes these items for international shipments.

CALIBRATORS

AxSYM PSA Master Calibrators (No. 7A49-30)

2 Bottles (4 mL each) of AxSYM PSA Master Calibrators contain PSA (human), nonreactive for anti-HIV-1/HIV-2 and HCV and nonreactive for HBsAg, prepared in TRIS buffer with protein stabilizers to yield the following concentrations:

Bottle	PSA Concentration (ng/mL)
1	0
2	10

Preservatives: Sodium Azide and Antimicrobial Agents.

AxSYM PSA Standard Calibrators (No. 7A49-01)/
PSA Calibrators (No. 9C04-01)

6 Bottles (4 mL each) of PSA Calibrators contain PSA (human), nonreactive for anti-HIV-1/HIV-2 and HCV and nonreactive for HBsAg, prepared in TRIS buffer with protein stabilizers to yield the following concentrations:

Bottle	PSA Concentration (ng/mL)
A	0
B	2
C	10
D	30
E	60
F	100

Preservatives: Sodium Azide and Antimicrobial Agents.

CONTROLS

AxSYM PSA Controls (No. 7A49-10)/
PSA Controls (No. 9C04-10)

3 Bottles (8 mL each) of PSA Controls contain PSA (human), nonreactive for anti-HIV-1/HIV-2 and HCV and nonreactive for HBsAg, prepared in TRIS buffer with protein stabilizers to yield the following concentration ranges:

Bottle	PSA (ng/mL)	Concentration Range (ng/mL)
L	4	3 - 5
M	15	12 - 18
H	45	36 - 54

Preservatives: Sodium Azide and Antimicrobial Agents.

SPECIMEN DILUENT

AxSYM PSA Specimen Diluent (No. 7A49-60)

1 Bottle (100 mL) PSA Specimen Diluent, Phosphate buffered goat serum. Preservatives: Sodium Azide and Antimicrobial Agents.

OTHER REAGENTS

Solution 1 (MUP) (No. 8A47-04)

4 Bottles (230 mL each) Solution 1 (MUP) containing 4-Methylumbelliferyl Phosphate, 1.2 mM, in AMP buffer. Preservative: Sodium Azide.

Solution 3 (Matrix Cell Wash) (No. 8A81-04)

4 Bottles (1000 mL each) Solution 3 (Matrix Cell Wash) containing 0.3 M Sodium Chloride in TRIS Buffer. Preservatives: Sodium Azide and Antimicrobial Agents.

Solution 4 (Line Diluent) (No. 8A46)

1 Bottle (10 L) Solution 4 (Line Diluent) containing 0.1 M Phosphate Buffer. Preservatives: Sodium Azide and Antimicrobial Agent.

AxSYM Probe Cleaning Solution
(No. 9A35-04/No. 9A35-05)

4 Bottles (110 mL each)/2 Bottles (220 mL each) AxSYM Probe Cleaning Solution containing 2% Tetraethylammoniumhydroxide (TEAH).

WARNINGS AND PRECAUTIONS

***For In Vitro* Diagnostic Use.**

SAFETY PRECAUTIONS

- **CAUTION:** This product contains human sourced and/or potentially infectious components. For a specific listing, refer to the **REAGENTS** section of this package insert. Product(s) should be handled as though capable of transmitting disease and found to be nonreactive for anti-HIV-1/HIV-2 and HCV and nonreactive for HBsAg. No known test method can offer complete assurance that products derived from human sources or inactivated microorganisms will not transmit infection. Therefore, all human sourced materials should be considered potentially infectious. It is recommended that these reagents and human specimens be handled in accordance with the OSHA Standard on Bloodborne Pathogens,[27] Biosafety Level 2[28] or other appropriate biosafety practices[29,30] should be used for materials that contain or are suspected of containing infectious agents.
- Reagents, Calibrators and Controls contain Sodium Azide as a preservative. Refer to Section 6, Chemical Hazards of the AxSYM System Operations Manual for the safe disposal of these materials.
- The AxSYM Probe Cleaning Solution (2% TEAH) may cause mild skin or eye irritation. If this solution comes in contact with skin, eyes or clothing, rinse immediately with water.

The Assay Diluent (Reagent Bottle 3), Master Calibrators 1 and 2 (List No. 7A49V and W), Calibrators (List No. 7A49 A-F and 9C04 A-F), Controls (List No. 7A49 L,M,N and 9C04 L,M,N), Specimen Diluent (List No. 7A49P), Solution 1 MUP (List No. 8A47-04), Solution 3 Matrix Cell Wash (List No. 8A81-04) and Solution 4 Line Diluent (List No. 8A46) of this product contain Sodium Azide and are classified per applicable European Economic Community (EEC) Directives as: Harmful (Xn). The following are the appropriate Risk (R) and Safety (S) phrases.

R22	Harmful if swallowed.
R32	Contact with acids liberates very toxic gas.
S2	Keep out of the reach of children.
S13	Keep away from food, drink and animal feedingstuffs.
S36	Wear suitable protective clothing.
S46	If swallowed, seek medical advice immediately and show this container or label.

HANDLING PRECAUTIONS

- **Do not use Solution 1 (MUP) beyond the expiration date or a maximum of 14 days on-board the AxSYM System. When loading new Solution 1 (MUP), it is important to immediately tighten the instrument cap**

for MUP to minimize exposure to air. Prolonged exposure of MUP to air may compromise performance.

* Do not use kits beyond the expiration date or a maximum of 112 cumulative hours on-board the AxSYM® System.
* Do not mix reagents from different reagent packs.

Refer to the AxSYM System Operations Manual, Sections 7 and 8, for a more detailed discussion of the safety and handling precautions during system operation.

STORAGE INSTRUCTIONS

The AxSYM PSA Reagent Pack, PSA Calibrators, PSA Controls and AxSYM PSA Specimen Diluent must be stored at 2-8°C (do not freeze). The AxSYM PSA Reagent Pack, Calibrators, Controls and Specimen Diluent may be used immediately after removing them from the refrigerator. Calibrators, Controls and Specimen Diluent should be returned to 2-8°C storage immediately after use. Reagents are stable until the expiration date when stored and handled as directed.

The AxSYM PSA Reagent Pack may be on-board the AxSYM System for a maximum of 112 cumulative hours; for example, 14 eight hour shifts. Refer to the AxSYM System Operations Manual, Sections 2 and 5, for further information on tracking on-board time.

Solution 1 (MUP) must be stored at 2-8°C. It may be on-board the AxSYM System for a maximum of 14 days. After 14 days, it must be discarded. It may be used immediately after removing it from the refrigerator. Do not freeze MUP.

The AxSYM Probe Cleaning Solution, Solution 3 (Matrix Cell Wash) and Solution 4 (Line Diluent) must be stored at 15-30°C.

INSTRUMENT PROCEDURE

Assay File Installation

The AxSYM PSA assay file must be installed on the AxSYM System from one of the following software disks prior to performing PSA assays:

* List No. 8A99-03, or higher (112 hours on-board Stability)
* List No. 3D50-01, or higher (112 hours on-board Stability)

Refer to the AxSYM System Operations Manual, Section 2, for proper installation procedures.

AxSYM PSA Assay Parameters

The default values for the visible assay parameters used for the AxSYM PSA assay are listed below. These parameters can be displayed and edited according to the procedure in the AxSYM System Operations Manual, Section 2. Press PRINT to print the assay parameters. Assay parameters that can be edited contain a (>) symbol. In order to obtain values for the parameters with an asterisk (*), review the specific Assay Parameter screen.

Assay Parameters

1 Long Assay Name (English): PSA
6 Abbrev Assay Name (English): PSA
11 Assay Number: 441
12 Assay Version: *
13 Calibration Version: *
14 Assay File Version: *
15 Assay Enabled> ON
17 Assay Type: MEIA
18 Standard Cal Reps> 2
19 Master Cal Reps: 0
20 Cal Adjust Reps: 0
21 Cal A Concentration: 0.00
22 Cal B Concentration: 2.00
23 Cal C Concentration: 10.00
24 Cal D Concentration: 30.00
25 Cal E Concentration: 60.00
26 Cal F Concentration: 100.00
27 Master Calibrator 1 Concentration: 0.00
28 Master Calibrator 2 Concentration: 10.00
29 Cal Adjust Concentration: 0
44 Default Calibration Method> Standard Calibration
45 Selected Result Concentration Units> ng/mL
46 Selected Result Decimal Places> 2
92 High Range Near: 100.00

Refer to the AxSYM System Operations Manual for a detailed description of Instrument Procedures.

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Only serum specimens may be used with the AxSYM PSA assay.

* Ensure that complete clot formation has taken place prior to centrifugation. Some samples, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time. If a serum sample is centrifuged before a complete clot forms, the presence of fibrin may cause erroneous results.
* Do not test grossly hemolyzed specimens.
* Avoid repeated freezing and thawing. Mix thoroughly after thawing, by low speed vortexing or gently inverting to ensure consistency in the results. Specimens showing particulate matter, erythrocytes, or turbidity must be clarified by centrifugation before testing.
* Samples may be stored for up to 24 hours at 2-8°C prior to being tested. If testing will be delayed more than 24 hours, the specimen should be stored at -20°C or colder. Samples that have been stored at -20°C or colder for 12 months have shown no performance differences.
* All samples (patient samples, controls and calibrators) should be tested within 3 hours of being placed on-board the AxSYM System. Refer to the AxSYM System Operations Manual, Section 5, for more detailed discussion of on-board sample storage constraints.
* Inspect all samples for bubbles. Remove all bubbles prior to analysis.
* When shipped, samples must be packaged and labeled in compliance with applicable federal and international regulations covering the transport of clinical samples and etiologic agents.

SAMPLE VOLUME

Sample volume required to perform a single PSA test on the AxSYM System varies according to the different sample containers. For sample cups, a ROUTINE test requires 150 µL, and a STAT test requires 123 µL. For every additional PSA test performed (ROUTINE or STAT) from the same container, an additional 73 µL of sample is required.

The sample cup minimum volumes for both STAT and ROUTINE tests are calculated by the AxSYM System. They are displayed on the Order screen at the time the test(s) is (are) ordered.

If the assay is configured for auto retest the additional sample volume needed for the retest will not be displayed on the screen at the time the test(s) is(are) ordered. Therefore, the total sample volume should include the additional 73 µL of sample.

To obtain the recommended volume requirements for the PSA Calibrators and Controls, hold the bottles **vertically** and dispense 4 drops of each Calibrator or Control into each respective sample cup.

Refer to the AxSYM System Operations Manual, Section 5, for volume requirements in primary or aliquot tubes and calibrator/control requirements for multiple reagent lots.

AxSYM® PSA PROCEDURE

Materials Provided

- No. 7A40-66 AxSYM PSA Reagent Kit, containing:
  - AxSYM PSA Reagent Pack
  - 100 reaction vessels
  - 100 matrix cells

Materials Required But Not Provided

- AxSYM System
- No. 7A49-10 AxSYM PSA Controls, or
- No. 9C04-10 PSA Controls
- No. 7A49-01 AxSYM PSA Standard Calibrators, or
- No. 7A49-30 AxSYM PSA Master Calibrators, or
- No. 9C04-01 PSA Calibrators
- No. 7A49-50 AxSYM PSA Specimen Diluent
- No. 8A47-04 Solution 1 (MUP)
- No. 8A81-04 Solution 3 (Matrix Cell Wash)
- No. 8A46 Solution 4 (Line Diluent)
- No. 9A35-04/ No. 9A35-05 AxSYM Probe Cleaning Solution
- No. 8A76-01 Sample cups

CAUTION:

- When manually dispensing sample into sample cups, verify that dispensing equipment does not introduce cross contamination and delivers specified sample volume.
- For optimal performance it is important to follow the routine maintenance procedures defined in the AxSYM System Operations Manual, Section 9. If your laboratory requires more frequent maintenance, follow those procedures.

Assay Procedure

Sections 5 and 6 of the AxSYM System Operations Manual can easily be removed for use at the instrument. They contain detailed steps for performing assay calibration and sample testing procedures.

Prior to ordering tests, confirm that the system inventory of matrix cells, bulk solutions and waste levels are acceptable.

The Orderlist Report contains sample placement information, sample volume requirements and sample cup volume requirements for all ordered tests. It is recommended that this report be referenced when loading samples into sample segments.

CAUTION: When operating the AxSYM System, always observe the following:

- The System status must be WARMING, PAUSED, READY or STOPPED before adding or removing sample segments, reagent packs or reaction vessels.
- Do not open the Interior Waste Door or the AxSYM Processing Center Cover while any test is in process. If opened, all processing will stop. Any tests will be terminated and must be repeated.
- When testing is completed, it is recommended that samples and the AxSYM PSA Reagent Pack be removed from the Sampling Center to maximize the on-board reagent pack use. Store at 2-8°C.

SAMPLE DILUTION PROCEDURES

Patient samples with a PSA value exceeding 100 ng/mL (HIGH RANGE, assay parameter 92), are flagged with the code ">100". To quantitate the concentration of these specimens, perform the "Manual Dilution" procedure.

Manual Dilution Protocol

A manual dilution can be performed by making a dilution of the specimen with the AxSYM PSA Specimen Diluent (No. 7A49-50) before pipetting the sample into the sample cup. It is desirable to perform the dilution so that the diluted specimen reads above 2 ng/mL on the calibration curve. Example: A ten-fold dilution is prepared by adding 100 µL of specimen to 900 µL of AxSYM PSA Specimen Diluent. Mix thoroughly before assaying. To determine the concentration of PSA in the specimen, multiply the concentration of the diluted sample by the dilution factor.

QUALITY CONTROL PROCEDURE

CALIBRATION

The AxSYM PSA assay must be calibrated using either a Master Calibration (2-point), or a Standard Calibration (6-point) procedure. The use of a particular calibration procedure is dependent on individual laboratory policy.

Master Calibration

Each AxSYM PSA Reagent Pack is shipped with a bar coded label insert that contains the Master Curve information for that specific lot of reagents. When using a new lot number for the first time, the bar coded Master Curve must be entered into the AxSYM System. Refer to the AxSYM System Operations Manual, Section 6, for additional information on entering Master Curve bar codes. Once this bar code information is entered, a Master Calibration must be performed.

To perform an AxSYM PSA Master Calibration, test Master Calibrators 1 and 2 in duplicate. A single sample of all levels of PSA controls must be tested as a means of evaluating the assay calibration.

Standard Calibration

The Standard Calibration procedure may be used without prior entry of the bar code Master Curve information. To perform an AxSYM PSA Standard Calibration, test Calibrators A, B, C, D, E, and F in duplicate. A single sample of all levels of PSA controls must be tested as a means of evaluating the assay calibration.

Once the AxSYM PSA Calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:

- A reagent pack with a new lot number is used.
- Control values are out of their specified range.

Refer to the AxSYM System Operations Manual, Section 6, for:

- Setting up an assay calibration
- When recalibration may be necessary
- Calibration verification

The AxSYM System verifies that the results of an assay calibration meet the specifications assigned to selected validity parameters. An error message occurs when the calibration fails to meet a specification. Refer to the AxSYM System Operations Manual, Section 10, for an explanation of the corrective actions for an error code. Refer to the AxSYM System Operations Manual, Appendices, for an explanation of the calibration validity parameters that may be used by the AxSYM System.

QUALITY CONTROL

The recommended control requirement for an AxSYM PSA assay is a single sample of the Low, Medium and High PSA Controls tested once every 24 hours. Controls may be placed in any position in the Sample Carousel.

If the quality control procedures in your laboratory require more frequent use of controls to verify test results, follow those procedures.

The PSA Control values must be within the acceptable ranges specified in the package insert (see **REAGENTS**, CONTROLS section).

INDICATIONS OF INSTABILITY OR DETERIORATION OF REAGENTS

When a PSA control value is out of the specified range, it may indicate deterioration of the reagents or errors in technique. Associated test results may be invalid and require retesting. Assay recalibration may be indicated.

Refer to the AxSYM® System Operations Manual, Section 10, for further troubleshooting information.

The AxSYM System has a capability to generate a Levey-Jennings plot of each assay's quality control performance. Refer to the AxSYM System Operations Manual, Section 5. At the discretion of the laboratory, selected quality control rules may be applied to the quality control data.

Fluorescence Background Acceptance Criteria

Quality control of the MUP substrate blank is automatically determined by the instrument and checked under Assay Parameter 64 (Max Intercept minus Max MUP Intercept) each time a test result is calculated. If the MUP intercept value is greater than the maximum allowable value, the result is invalid. The test request will be moved to the Exceptions List where it will appear with the message "1064 Invalid test result, intercept too high" and the calculated intercept value. Refer to the AxSYM System Operations Manual, Section 10, when this error message is obtained.

Refer to the AxSYM System Operations Manual, Section 2, for further information on this parameter.

RESULTS

AxSYM PSA utilizes a four parameter logistic curve fit (4PLC Analysis) to generate a Standard Calibration curve and a Ratio A Technique to generate the instrument-specific Master Calibration.

Flags

Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the AxSYM System Operations Manual, Section 2.

LIMITATIONS OF THE PROCEDURE

Serum PSA concentrations should not be interpreted as absolute evidence for the presence or absence of prostatic cancer. Elevated concentrations of PSA may be observed in the serum of patients with benign prostatic hyperplasia or other nonmalignant disorders as well as in prostate cancer. Furthermore, low PSA concentrations are not always indicative of the absence of cancer. The PSA value should be used in conjunction with information available from clinical evaluation and other diagnostic procedures such as DRE. Some early cases of prostate cancer will not be detected by PSA testing, the same is true for DRE. Prostatic biopsy is required for the diagnosis of cancer.

- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies.[91-93] These specimens should not be assayed with the AxSYM PSA assay.
- Heterophilic antibodies in serum have the potential to cause interference in immunoassay systems.[94,95] Infrequently, PSA levels may appear elevated due to heterophilic antibodies present in the patient's serum or to nonspecific protein binding. If the PSA level is inconsistent with clinical evidence, additional PSA testing is suggested to confirm the result.
- The concentration of PSA in a given specimen, determined with assays from different manufacturers, can vary due to differences in assay methods, calibration, and reagent specificity.[25,96] PSA in serum and in seminal fluid may exist in different forms. Quality control samples may be produced by introducing seminal fluid PSA into a human serum matrix. The concentration of PSA in these controls determined with assays from different manufacturers can vary due to differences in assay methods, calibration, reagent specificity and the form of PSA that is present; therefore, it is important to use assay-specific values to evaluate quality control results.
- Specimens obtained from patients immediately following digital rectal examination show no clinically significant increases in PSA levels.[97] However, prostatic massage, ultrasonography and needle biopsy may cause clinically significant elevations.[98] Hormonal therapy may affect PSA expression; therefore, a low PSA level after any treatment that includes hormonal therapy may not adequately reflect the presence of residual or recurrent disease.

EXPECTED VALUES IN DETECTION OF PROSTATE CANCER

A retrospective study was conducted at nine clinical sites to demonstrate the usefulness of PSA in the detection of prostatic cancer when used in conjunction with DRE. All clinical data presented supporting the detection claim were generated using the IMx® Analyzer and IMx PSA assay reagents. A total of 4,570 men 50 years of age or older participated in the study. A distribution of the initial testing results is presented in Table 1.

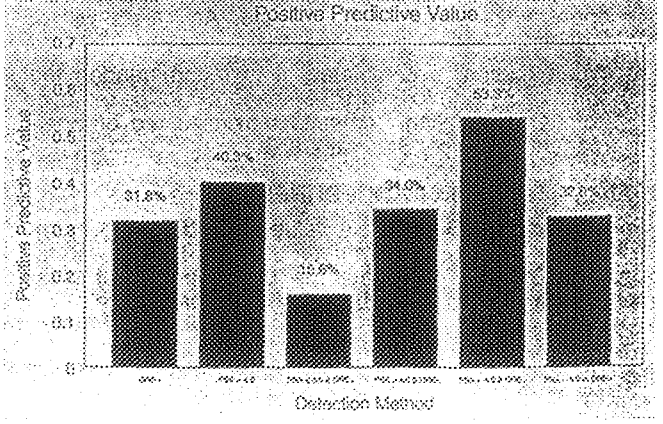
Table 1.
Distribution of Results from Initial Testing

	PSA ≥ 4.0	PSA < 4.0	Total
DRE+	125	266	391
%	2.7%	5.8%	8.6%
DRE-	436	3,743	4,179
%	9.5%	81.9%	91.4%
Total	561	4,009	4,570
%	12.3%	87.7%	100%

Note: 827 Patients Tested Positive by DRE and/or PSA

DRE = Digital Rectal Examination
Key: + = Suspicious for Cancer
- = Not Suspicious for Cancer

The study demonstrated that PSA levels were more predictive of prostate cancer than DRE alone. The positive predictive value was 10.3% for elevated levels of PSA (≥4.0 ng PSA/mL) and 31.8% for a suspicious DRE. When PSA levels were ≥4.0 ng PSA/mL but the DRE was not suspicious, the positive predictive value was 34.0%. When the DRE was suspicious but the PSA level was <4.0 ng PSA/mL, the positive predictive value was 15.6%. When both tests were suspicious for cancer, the positive predictive value was 53.3%. This is presented graphically.



Of the 4,570 subjects studied, 405 were biopsied based on an elevated PSA or a suspicious DRE. The percentage of biopsied subjects with cancer corresponding to PSA and DRE results are shown in Table 2.

Table 2
Positive Predictive Values

Detection Method	Positive Predictive Value*	Number of Biopsied Subjects with Cancer
DRE+	31.0% (25.5% - 36.0%)	68/214
PSA > 4.0	40.3% (34.6% - 46.0%)	94/293
PSA > 4.0 DRE+	35.6% (29.1% - 42.0%)	49/122
PSA > 4.0 DRE-	34.0% (27.3% - 40.8%)	45/191
PSA > 4.0 DRE+	53.3% (43.1% - 63.5%)	49/92
PSA > 4.0 or DRE+	32.8% (28.5% - 37.4%)	133/405

*95% Confidence Interval (Lower Limit - Upper Limit)

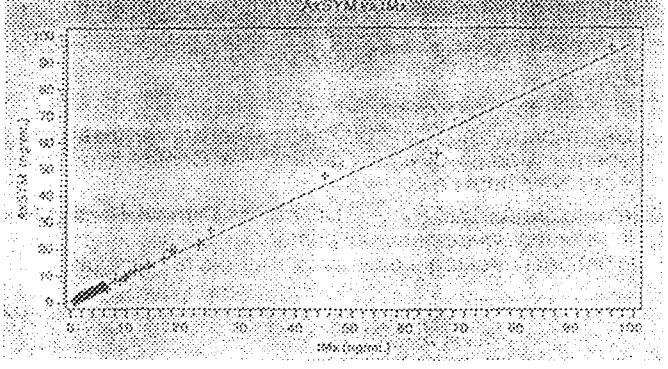
Of the 405 subjects who underwent biopsy, 155 cancers were detected. The overall cancer detection rate was 3.94% for either test, 1.46% for both tests, 4.94% for PSA alone and 2.72% for DRE alone. These results are shown in Table 3.

Table 3
Cancer Detection Rate

Detection Method	Cancer Detection Rate*	Calculation*
DRE+	2.72%	68/(361/214) / 4570
PSA > 4.0	3.94%	155/(293) / 4570
PSA > 4.0 & DRE+	1.46%	49/(125/92) / 4570
PSA > 4.0 or DRE+	3.94%	155/(361/405) / 4570

*Cancer Detection Rate = Number of Cancers Found by Test / Total Number of Subjects Tested

To show that the performance of the AxSYM® PSA assay reagents give comparable results, an equivalency study was performed on 1,125 specimens. The values obtained using the IMx® PSA assay were compared to values obtained using the AxSYM PSA assay on their respective systems. Linear regression analysis was performed on the PSA values. The regression analysis for all specimens (n=1,125) covering the complete range of PSA values observed (0.100 ng/mL) yielded a correlation coefficient of 0.997, a slope of 0.96 and a y-intercept of 0.0. These results demonstrate that the AxSYM PSA assay system yields equivalent results to those obtained with the IMx assay system.



Serum PSA concentrations, regardless of the value, should not be interpreted as definitive evidence for the presence or absence of prostate cancer. In addition, PSA testing should be done in conjunction with DRE because PSA and DRE together detected the greatest number of cancers. Prostate biopsy is required for the diagnosis of cancer.

EXPECTED VALUES FOR PROGNOSIS AND MANAGEMENT

The distribution of PSA values determined in 1,508 specimens is shown in the following table.

Distribution of PSA Values

	Number of Subjects	Percent (%) 0-4.0 ng/mL	4.1-10 ng/mL	10.1-30 ng/mL	30.1-60 ng/mL	>60 ng/mL
HEALTHY SUBJECTS						
Males >40 yrs	106	96.0	3.5	0.5	0.0	0.0
Males <40 yrs	199	100.0	0.0	0.0	0.0	0.0
MALIGNANT DISEASES						
Prostate						
Stage A	65	60.0	30.8	7.7	0.0	1.5
Stage B	88	37.5	28.1	25.0	5.4	9.1
Stage C	192	19.7	23.7	30.8	10.6	15.0
Stage D	136	14.7	11.8	16.2	16.3	47.1
Genitourinary	120	88.3	10.0	1.7	0.0	0.0
NONMALIGNANT DISEASES						
BPH	209	76.5	16.5	4.3	1.0	0.0
Prostatitis	80	81.3	12.5	6.2	0.0	0.0
Genitourinary	101	86.1	8.9	5.0	0.0	0.0
Renal	102	67.3	19.6	3.9	6.9	0.0
Cirrhosis	58	91.4	8.6	0.0	0.0	0.0

In this study, 98% of the specimens from normal males (n=397) had values of 4.0 ng/mL or less.

It is recommended that each laboratory establish its own expected reference range for the population of interest.

The distribution table is derived primarily from monitored carcinoma patients representing both active (clinical evidence of disease progression) and inactive (no clinical evidence of disease progression) disease states. When changing PSA assay methods, in the course of monitoring a patient, additional sequential testing should be carried out to confirm baseline values.

SPECIFIC PERFORMANCE CHARACTERISTICS

PRECISION

Precision was determined as described in National Committee for Clinical Laboratory Standards (NCCLS) Protocol EP5-T2.[40] A five member serum based panel was assayed at 3 laboratories (N=80 for each panel) in replicates of 2 at two separate times per day for twenty days using a single lot of reagents and a single calibration. Data from this study are summarized in the following table.

Reproducibility of AxSYM PSA

	Lab	Mean PSA (ng/mL)	Within Run (%) CV	Between Run (%) CV	Between Day (%) CV	Total (%) CV
Panel 1	1	0.56	5.4	0.0	1.9	5.7
	2	0.54	5.3	1.6	3.7	6.7
	3	0.57	3.9	3.4	4.5	6.9
Panel 2	1	6.1	3.8	2.2	3.5	5.0
	2	6.2	3.0	0.0	4.0	5.6
	3	6.2	4.0	2.1	4.7	6.6
Panel 3	1	18.8	3.7	0.0	2.1	4.3
	2	19.1	3.6	1.1	3.4	5.0
	3	19.2	4.4	0.0	4.6	6.3
Panel 4	1	44.2	4.2	2.1	1.5	4.9
	2	44.1	3.8	2.3	3.5	5.8
	3	45.0	3.3	4.5	4.7	7.3
Panel 5	1	69.1	4.1	4.2	1.0	5.9
	2	69.1	5.1	2.6	2.3	6.2
	3	70.6	4.6	4.4	4.2	7.5

The standard deviation may be calculated by multiplying the mean PSA concentration by the percent CV and dividing by 100.

$$SD = \frac{\text{Mean (ng/mL)} \times (\%)\ CV}{100}$$

RECOVERY

Known concentrations of serum PSA were added to normal human serum samples. The concentration of PSA was determined using the AxSYM® PSA assay and the resulting percent recovery was calculated.

Recovery of PSA

Sample	Endogenous Level (ng/mL)	PSA Added (ng/mL)	Value Obtained (ng/mL)	(%) Percent Recovery*
NORMAL HUMAN SERUM	4.0	6.4	10.5	102
		30.9	34.8	100
	13.4	6.9	20.0	96
		30.6	44.0	98

$$\%\ \text{Recovery} = \frac{\text{PSA Value Obtained (ng/mL)} - \text{Endogenous Level (ng/mL)}}{\text{PSA Added (ng/mL)}} \times 100$$

SENSITIVITY

The sensitivity of the AxSYM PSA assay was calculated to be better than 0.1 ng PSA/mL. This sensitivity is defined as the concentration at two standard deviations above the PSA Calibrator A (0 ng/mL), and represents the lowest measurable concentration of PSA that can be distinguished from zero.

SPECIFICITY

The specificity of the AxSYM PSA assay was determined by testing sera containing the compounds listed in the following table. These compounds did not show interference in the AxSYM PSA assay at the levels indicated.

INTERFERING SUBSTANCES

Test Compound	Test Concentration
Bilirubin	50 mg/dL
Hemoglobin	1000 mg/dL
IgG	3000 mg/dL
Protein	3-14 g/dL
Triglycerides	3000 mg/dL

CHEMOTHERAPEUTIC AGENTS

Test Compound	Test Concentration
Cyclophosphamide	700 µg/mL
Diethylstilbestrol	2 µg/mL
Doxorubicin-HCl	16 µg/mL
Estramustine phosphate	200 µg/mL
Flutamide	10 µg/mL
Goserelin Acetate	100 ng/mL
Lupron®	100 µg/mL
Megestrol acetate	90 µg/mL
Methotrexate	30 µg/mL

CARRYOVER

No significant carryover (less than 0.003%) was detected when a sample containing 70,000 ng/mL of PSA was assayed.

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Prostate Cancer

What Everyone Should Know

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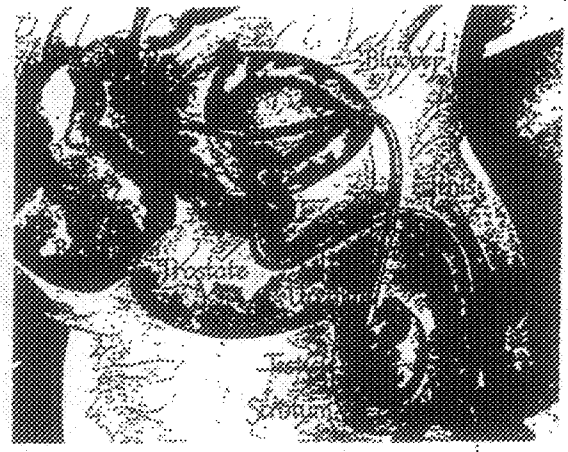
This brochure will educate you about prostate cancer – how it develops, its effects and available treatment options. While this material will answer most of your questions, you will probably have some remaining concerns that would best be answered by your physician. We encourage you to discuss those questions with him or her. Some medical terms contained within this material may be unfamiliar to you. These words have been highlighted in the text, and a complete list of definitions can be found at the end of the brochure.

What is Cancer?

Cancer is a disease characterized by the uncontrolled growth and spread of abnormal body cells. The human body is made up of billions of cells. Normally, cells reproduce themselves by dividing so that growth occurs. Worn-out tissues are replaced and injuries are repaired in this manner. Occasionally, cells abnormally grow into a mass called a tumor. Some tumors are benign (noncancerous); others are malignant, or cancerous.

The growth of a benign tumor may interfere with body function, but these tumors are seldom life-threatening. Malignant tumors, on the other hand, invade and destroy normal tissue. By a process called metastasis, cells break away from a cancerous tumor and spread through the blood and lymphatic system to other parts of the body where they form new tumors. Sometimes cancer grows and spreads rapidly. In other cases, it develops and spreads slowly.

One common place for cancer to develop in men is the prostate gland.



The prostate and surrounding organs

What is the Prostate?

The prostate is a chestnut-sized sex gland. It is located just below the bladder and surrounds part of the urethra, the canal that carries urine from the bladder during urination. The primary role of the prostate is to provide part of the fluid necessary for ejaculation.

How Common is Prostate Cancer?

According to the American Cancer Society, there are more than 100 different types of cancer. Among American men, prostate cancer is the second most common cause of cancer death. The risk of developing prostate cancer increases with age: it typically occurs in men age 40 and above. In fact, the American Cancer Society recommends that all men over age 40 have a yearly medical check-up that includes a rectal exam. Yearly exams may help physicians detect prostate cancer at an early, treatable stage.

Symptoms of prostate cancer are often associated with benign prostate hypertrophy (BPH). Both conditions are common in older men, and one of the signs of both is the urge to urinate more often, which results from the prostate's increased size. BPH is an excess growth in the innermost part of the prostate. It is not cancer. The only way to distinguish between BPH and prostate cancer is to have an examination by a physician.

What Causes Prostate Cancer?

The exact cause of prostate cancer is unknown. What is known about the disease is that it begins with a group of cancerous cells (a tumor) within the prostate gland. Initially, the tumor may not cause any symptoms. As the cancer progresses, the tumor can enlarge and eventually put pressure on surrounding parts of the body such as the urethra. This process causes a block in the flow of urine out of the bladder. At this stage of the disease, many men urinate more frequently than normal (usually the first symptom of the disease); sometimes the urination is difficult, even painful.

Are There Other Symptoms?

Other symptoms of prostate cancer include blood or pus in the urine or semen and/or painful ejaculation. It is important to remember that prostate cancer, especially in its early stages, may not produce any symptoms at all. This is why regular examinations are recommended. As prostate cancer spreads from the prostate to nearby lymph nodes, bones or other organs, many men experience aches and pain in their bones or joints, especially in the back and hips.

Why Does Prostate Cancer Spread?

The growth and function of the normal prostate gland is dependent on the male hormone testosterone. Testosterone is produced almost entirely by the testicles, although small amounts are also produced by the adrenal glands. Testosterone stimulates prostate cancer much in the same way kerosene fuels a fire. As long as the body produces testosterone, prostate cancer will continue to grow and spread.

How is Prostate Cancer Detected?

Doctors currently use a variety of methods to detect the presence of prostate cancer.

The most common method of detecting prostate cancer is through an examination of the rectum. To examine the prostate, a physician inserts a lubricated, gloved finger into the patient's rectum to feel the size and shape of the prostate through the rectum wall. This procedure, called a digital rectal examination, takes very little time (less than a minute) and involves minimal discomfort to the patient.

There are a variety of ways to detect and monitor prostate cancer

The PSA blood test is a simple laboratory procedure. A blood sample is tak and sent to a laboratory where it is tested using the PSA test. The PSA test measure the amount of PSA that is in your blood. You should know that levels of PSA do not always indicate the presence or absences of prostate ca

A result of 0- 4 ng/mL is generally considered a normal PSA level. Howeve many men with PSA levels greater than 4.0 ng/mL do not have prostate canc Likewise, a PSA level less than 4.0 ng/mL does not rule out the possibility of prostate cancer.

It has been recommended that men 50 years of age or older have a PSA test and DRE to help the physician detect the possible presence of prostate cance These tests can be done during a yearly physical examination.

An important fact to know is that when the PSA test is used in conjunction w the digital rectal examination the two tests together are more effective in dete prostate cancer than when either test is used alone.

There is always the possibility that some cancers may go undetected. This is because some cancers may be too small to be felt during digital rectal exam or raise the level of PSA. There is also the chance that a healthy man may be identified as having prostate cancer. If the PSA result is elevated or the digita rectal examination is suspicious for cancer further diagnostic follow-up is recommended.

Another common procedure used in conjunction with the digital rectal examination, is a blood test which measures prostate specific antigen (PSA). Prostate specific antigen is a protein which is only produced by the prostate gland Small amounts of PSA may be present in the blood and can be measured by the PSA test. When the body's PSA levels are elevated, it may be an indicator to the physician of possible prostate disease including:

benign prostatic hyperplasia (BPH) This is an enlargement of the prostate gland which is very common in men over 50 years of age and may cause difficulty with urination

prostatitis which is an infection or inflammation of the prostate gland.

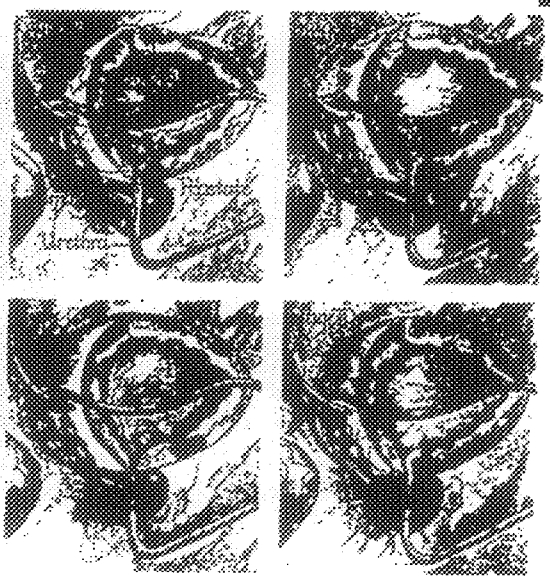
prostatic cancer

Another way to detect prostate cancer is through the use of ultrasound. During this procedure, a physician places a small instrument into the rectum which produces painless soundwaves that reflect off the prostate. The reflected sound waves are then transformed into an image of the prostate on a television screen which the physician can view.

If prostate cancer is suspected, the physician may remove a small sample of prostate tissue through a needle biopsy. The tissue sample is then examined under a microscope to determine whether it contains cancer cells. This is the only way to definitively diagnose prostate cancer.

What are the Stages and Treatment Options for Prostate Cancer?
It is important that the physician determine the extent or stage of the patient's prostate cancer so that the best treatment option can be pursued. The treatment of prostate cancer depends on the stage of the tumor. In developing a treatment plan, it is important that the patient and physician discuss the advantages and disadvantages of each treatment. The following are detailed descriptions of the four stages of prostate cancer and treatment options:

•Stage A--The tumor is located within the prostate gland and is too small to be detected during a rectal examination, but may be detected through other diagnostic procedures. This stage of prostate cancer generally produces no symptoms and treatment can be considered "curative." A patient has several treatment options if diagnosed with Stage A prostate cancer. Treatment options include surgical removal of the prostate or radiation therapy.



The four stages of prostate cancer

Surgical Removal of the Prostate --
A procedure called a prostatectomy (removal of the prostate) can be performed to prevent early-stage prostate cancer from spreading further. During this procedure, a pelvic node dissection (removal of possible cancer carrying lymph nodes near the prostate) is often performed. Side effects associated with prostatectomy may include impotence and incontinence. Impotence occurs in a high percentage of patients; however, new surgical techniques are minimizing this risk. As in any surgical procedure, complications can occur which require further attention.

Radiation Therapy – This process uses high-energy x-rays to kill prostate cancer cells. As an alternative, small nonhazardous radioactive pellets can be surgically implanted into the patient's prostate. This form of therapy is good for patients who wish to avoid an operation and the possible risk of incontinence and impotence. Side effects with radiation therapy include fatigue, skin reactions in treated areas, frequent and painful urination, upset stomach, diarrhea and rectal irritation or bleeding. Most of these side effects disappear once treatment is stopped.

•Stage B--The tumor is still located within the prostate gland, but it has grown to the point where it can be felt during a rectal examination. There are often no symptoms associated with prostate cancer at this stage. Treatment for Stage B prostate cancer can be considered "curative." Common treatment options in this stage include surgical removal of the prostate and radiation therapy (see Stage A for detailed descriptions).

•Stage C--The tumor has spread from the prostate to other areas just around the prostate. A common symptom in this stage is difficulty in urinating. Some physicians may elect to treat the cancer by surgical removal of the prostate, radiation therapy or a combination of each (see Stage A for detailed descriptions).

Surgery is one option available to prostate cancer patients

The objective of treatment in Stage C is to slow the spread of prostate cancer and relieve symptoms such as pain and difficulty in urinating.

Another treatment option in Stage C is hormonal therapy. The goal of hormonal therapy is to decrease the testicles' production of testosterone, which fuels prostate cancer. Hormone manipulation cannot cure prostate cancer, but it can slow the cancer's growth, reduce the size of the tumor and alleviate the symptoms associated with the disease. There are several methods to reduce the body's production of testosterone.

Surgical Removal of the Testicles -- Traditional treatment for advanced prostate cancer has involved the surgical removal of the testicles. The medical term for this type of surgery is orchiectomy. An orchiectomy can be done as an in-or-out-patient procedure, but it may require hospitalization and general anesthesia. During the procedure, a surgeon removes the patient's testicles. Removal of the testicles effectively reduces the production of testosterone and relieves the pain, difficulty in urination and other symptoms associated with prostate cancer. Common side effects include impotence and hot flashes.

LH-RH (Leutinizing Hormone-Releasing Hormone) Analogs -- A newer treatment option, LH-RH analogs, are man-made adaptions of a natural occurring hormone, which aid in the production of testosterone. When taken monthly, LH-RH analogs shut down testosterone production from the testicles. LH-RH analog treatment is also effective in relieving the pain, difficulty in urinating and other symptoms associated with prostate cancer.

Preferably, LH-RH analogs are administered as a once-a-month injection while in the physician's office. A daily, self-administered injection is also available. The most common side effect associated with LH-RH analog treatment is hot

A newer treatment option for patients with advanced prostate cancer is LH-RH analogs

flashes. Some men may also experience a temporary increase in their urinary symptoms or pain during the first few weeks of treatment. Like other treatment options, LH-RH analogs may cause impotence.

Combination Therapy -- Another treatment alternative for advanced prostate cancer patients involves the use of a hormone-blocking drug, taken orally on a daily basis, in conjunction with an LH-RH analog. The LH-RH analog stops the production of testosterone by the testicles, while the hormone-blocking drug blocks the small additional amount of

testosterone produced by the adrenal glands. Side effects of combination therapy include hot flashes, nausea and vomiting, diarrhea and impotence.

Female Hormones – Another way to decrease the production of testosterone by the testicles is by taking the female hormone, estrogen. Estrogen therapy is relatively simple and involves taking a tablet one to three times a day. Estrogen works by counteracting the male hormone testosterone. Although effective in reducing testosterone levels, the side effects of female hormone therapy can include water retention, breast growth and tenderness, stomach upset, nausea and vomiting. In addition, this therapy may cause or increase serious circulatory system problems, such as blood clots and stroke.

•Stage D–The tumor has spread to other parts of the body such as the bones or lymph nodes. Common symptoms in this stage include difficulty in urinating, bone pain, weight loss and fatigue. Surgery and hormonal therapy (see Stage C for detailed descriptions) are common treatment options in this advanced stage of prostate cancer. In addition, chemotherapy may be used, usually after multiple forms of therapy have been tried. The goal of treatment in Stage D prostate cancer is to relieve pain, difficulty in urinating and other symptoms.

Chemotherapy – Chemotherapy is the use of anticancer drugs which circulate throughout the body in the blood stream and kill rapidly growing cells. This includes cancer cells as well as some normal, healthy ones. To minimize harm to healthy cells, the antineoplastic agents are carefully controlled in dosage and frequency. There are a variety of chemotherapy drugs which are often used in combination with one another. They are used mainly to relieve the symptoms of advanced prostate cancer. There are many side effects associated with chemotherapy.

What Treats Prostate Cancer?

If prostate problems are discovered, a physician may refer the patient to a specialist called a urologist. A urologist is a physician and surgeon who is specially trained in the diagnosis and treatment of diseases of the urinary tract and genital tract in patients of any age or sex. The urologist will determine if a patient's prostate symptoms are caused by prostate enlargement or prostate cancer. In some cases, a patient may be referred to an oncologist, a specialist in the treatment of cancer. Treatment options should be fully understood and discussed with a physician so that a treatment course can be agreed upon.

How Does One Cope with Prostate Cancer?

It is natural for a man who first learns that he has prostate cancer to feel angry, anxious and uncertain. These same feelings are often experienced by family members and close friends. One of the best ways to deal with these feelings is to talk about them openly and honestly with other prostate cancer patients and families who share similar experiences. Since the problems are similar, support and encouragement can be provided. You may wish to ask your physician to put you in touch with other patients who would be willing to discuss their situation with you. Sometimes these discussions take place in the form of Prostate Cancer Support Groups. Consult your physician to learn if there are any support groups in your area.

How to Receive More Information on Prostate Cancer

The American Foundation for Urologic Disease, Inc. (AFUD) has formed a support group (US TOO) for prostate cancer patients. To learn more about prostate cancer, AFUD and US TOO you can call 1-800-242-2383 or write to:

American Foundation for
Urologic Disease, Inc.
1120 North Charles Street, Suite 401
Baltimore, MD 21201

One of the best ways to deal with feelings is to discuss them openly and honestly with others who are having similar experiences.

The American Cancer Society (ACS) and the National Cancer Institute (NCI) can also provide you with additional information free of charge by calling your local ACS office or by calling the NCI's toll-free Cancer Information Service (1-800-4-CANCER) or by writing to:

Office of Cancer Communications
National Cancer Institute
Building 31, Room 10A24
9000 Rockville Pike
Bethesda, MD 20892

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Definition of Medical Terms

Adrenal glands: Located near the kidneys, the adrenal glands produce a small amount of the male hormone, testosterone.

Benign tumor: A tumor which is noncancerous.

Biopsy: The removal of tissue from the body for diagnostic examination.

Digital rectal examination: A common screening procedure for prostate cancer whereby a physician inserts a gloved, lubricated finger into the rectum in order to feel the size and shape of the prostate through the rectal wall.

Ejaculation: A sudden release of fluid, especially of semen, from the body.

Estrogen: A female sex hormone.

Impotence: The inability to have an erection.

Incontinence: A loss of urinary control.

LH-RH analogs: Man-made compounds that are similar to the natural leutinizing hormone-releasing hormone which aids in the production of testosterone.

Lymph nodes: Small bean-shaped structures scattered along the vessels of the lymphatic system. The lymph nodes produce white blood cells and filter bacteria and cancer cells that may travel through the system.

Malignant tumor: A tumor which is cancerous.

Metastasis: The spread of disease from one part of the body to another.

Oncologist: A specialist in the treatment of cancer.

Orchiectomy: Surgical removal of the testicles.

Pelvic node dissection: Removal of cancer carrying lymph nodes near the prostate for their evaluation.

Prostate specific antigen: A substance manufactured only by the prostate.

Prostate specific antigen test: A blood test which measures a patient's level of prostate specific antigen. If elevated the test may be an indicator of prostatic cancer.

Prostatic acid phosphatase test: A blood test for a substance that rises above normal in many patients when prostate cancer has spread beyond the prostate.

Prostatectomy: Surgical removal of the prostate.

Rectum: The last five or six inches of the intestine leading to the outside of the body.

Semen: A thick whitish fluid secreted by the prostate to carry sperm.

Stage: A term used to describe the extent of cancer.